



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/72, 31/35		A1	(11) International Publication Number: WO 98/31353
			(43) International Publication Date: 23 July 1998 (23.07.98)
(21) International Application Number: PCT/SE98/00041 (22) International Filing Date: 13 January 1998 (13.01.98)		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: 9700136-6 20 January 1997 (20.01.97) SE		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant (<i>for all designated States except US</i>): ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (<i>for US only</i>): TROFAST, Jan [SE/SE]; Vapenkroken 34, S-226 47 Lund (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).			
(54) Title: NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF FROM 0.28 TO 0.38 G/ML, COMPRISING TERBUTALINE SULPHATE, A PROCESS FOR PREPARING THE FORMULATION AND THE USE THEREOF			
(57) Abstract A dry powder composition comprising terbutaline sulphate and a carrier substance, both of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml is useful in the treatment of respiratory disorders.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF FROM 0.28 TO 0.38 G/ML, COMPRISING TERBUTALINE SULPHATE, A PROCESS FOR PREPARING THE FORMULATION AND THE USE THEREOF

Field of the Invention

The present invention provides a new pharmaceutical formulation, its preparation and its
5 use.

Background to the Invention

Potent drugs for administration by inhalation are generally formulated in association with carriers such as lactose because of the problem of preparing accurate doses. When such
10 drugs are diluted, variations in the weight of the formulation result in a smaller drug dosage variation rate compared with when they are not diluted. These formulations have generally consisted of coarse particles of the carrier with fine particles of the drug, which combination is generally known as an ordered mixture.

15 The invention provides an improved formulation which, in systems designed to imitate inhalation has been found to give an improved dispersion of the drug.

Description of the Invention

According to the invention there is provided a dry powder composition comprising
20 terbutaline sulphate and a carrier substance, both of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml.

The poured bulk density according to the present invention is measured using known techniques, for example those described in "Powder testing guide: Methods of measuring
25 the physical properties of Bulk powders" L. Svarovsky, Elsevier Applied Science 1987, pp 84-86.

The carrier substance is preferably a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers are, for example, lactose, glucose, raffinose, melezitose,

lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Lactose is particularly preferred, especially in the form of its monohydrate.

- The ingredients of the formulation according to the invention must both be in a finely divided form, i.e. their mass median diameter should generally be less than 10 µm, preferably from 1 to 7 µm, as measured by a laser diffraction instrument or a coulter counter. The ingredients may be produced in the desired particle size using methods known to those of skill in the art, e.g. milling, micronisation or direct precipitation.
- 10 The composition according to the invention is preferably formulated to comprise, as a daily dose, from 50 µg to 8 mg, more preferably from 100 µg to 4 mg and most preferably from 125 µg to 2 mg of terbutaline sulphate. More preferably the composition is formulated to provide unit doses of 125, 250 or 500 µg of terbutaline sulphate. The composition is preferably formulated to comprise in each unit dose from 50 µg to 25 mg of the carrier substance, more preferably from 50 µg to 10mg, most preferably from 100 to 4000 µg.
- 15

According to the invention there is further provided a process for preparing a composition according to the invention which comprises

- (a) micronising terbutaline sulphate and the carrier substance;
- 20 (b) optionally conditioning the product; and
- (c) spheronizing until the desired bulk density is obtained.

The process preferably further comprises a low energy remicronisation step after step (b).

- 25 The formulation according to the invention may be made by conventional techniques known *per se*. Such production processes generally comprise micronising the ingredients to the required size, removing any amorphous areas on the particles obtained by, for example, the methods described in WO 92/18110 or WO 95/05805 and then agglomerating, spheronising and sieving the powder obtained. The size of the agglomerates obtained is preferably in the range of from 100 to 2000 µm, more preferably from 100 to 800 µm. The bulk density of the formulation produced may be adjusted by
- 30

varying the components and the process empirically, for example the bulk density can be increased by lengthening the time in which the particles are tumbled in a spheronising device.

- 5 In solid-solid mixing, one of the most important features is to ensure content uniformity. The major problem encountered in the powder mixing of fine powders is the inability of mixers to break down powder agglomerates. It has been found that a remicronisation step after the conditioning step of the fine powder with low energy input is advantageous. It should generally be carried out using enough energy to break down powder agglomerates
- 10 but not with so much energy that the size of the particles themselves is affected. Such a step gives a composition wherein the active substance and carrier substance are substantially uniformly distributed, having for example a relative standard deviation of less than 3% (preferably less than 1%) and does not disturb the crystallinity of the fine particles.
- 15 The formulation according to the invention may be administered using any known dry powder inhaler, for example the inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler, for example Turbuhaler (trade mark). The invention further provides use of a composition according to the invention in the manufacture of a medicament for use in therapy. The composition according to the invention is useful in the
- 20 treatment of respiratory disorders, particularly asthma. The invention also provides a method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according to the invention.
- 25 The invention is illustrated, but not limited, by reference to the following Examples.

Example 1

60 Parts of terbutaline sulphate were micronized to a mass medium diameter of less than 2 μm in a Alpin mill 100AFG and thereafter conditioned according to the method described

in US 5562923. 40 Parts of lactose monohydrate were micronized (Alpin mill 100AFG) down to a mass medium diameter of less than 3 μm and thereafter conditioned according to the method described in WO 95/05805. The micronized and conditioned terbutaline sulphate and lactose monohydrate were mixed thoroughly in a Turbula mixer. The mixture was remicronised in a spiral jet mill at a pressure of only about 1 bar to obtain an evenly distributed mixture. The powder was then agglomerated by feeding the powder into a twin screw feeder (K-Tron), sieving in an oscillating sieve (0.5 mm mesh size), spheronising in a rotating pan with a peripheral speed of 0.5m/s for 4 minutes and then sieving again using the same sieve, then spheronising once more for 6 minutes before final sieving (mesh size 1.0 mm) giving a powder with a bulk density of 0.28 g/ml.

Example 2

Example 1 was repeated with 30 parts of terbutaline sulphate and 70 parts of lactose monohydrate to give a powder with a bulk density of 0.31 g/ml.

Claims

1. A dry powder composition comprising terbutaline sulphate and a carrier substance, both of which are in finely divided form, wherein the formulation has a poured bulk density
5 of from 0.28 to 0.38 g/ml.
2. A composition according to claim 1 wherein the bulk density is from 0.30 to 0.36 g/ml.
- 10 3. A composition according to claim 1 or 2 wherein the active substance and carrier substance are substantially uniformly distributed.
4. A composition according to claim 1, 2 or 3 for use in the treatment of a respiratory disorder.
- 15 5. A process for preparing a composition according to claim 1 which comprises
 - (a) micronising terbutaline sulphate and the carrier substance;
 - (b) optionally conditioning the product; and
 - (c) spheronizing until the desired bulk density is obtained.
- 20 6. A process according to claim 5 which comprises a low energy remicronisation step after step (b).
7. Use of a composition according to claim 1, 2 or 3 in the manufacture of a medicament
25 for use in therapy.
8. A method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according to claim 1, 2 or 3.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00041

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/72, A61K 31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, USPATFULL, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4590206 A (RAYMOND B. FORRESTER ET AL), 20 May 1986 (20.05.86), column 4, line 15 - line 21; column 4, line 46 - line 47 --	1-8
X	US 5551489 A (EVA A. C. TROFAST ET AL), 3 Sept 1996 (03.09.96), column 2, line 8 - line 15 -----	1-8

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

13 May 1998

19 -05- 1998

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86Authorized officer
Anneli Jönsson
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00041

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claim 8 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/04/98

International application No.

PCT/SE 98/00041

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4590206 A	20/05/86	AU 540826 B AU 8635582 A BE 893912 A CA 1187415 A CH 657273 A,B DK 159716 B,C DK 325982 A EP 0072046 A,B SE 0072046 T3 FI 822548 A FR 2510405 A GB 2105189 A,B HK 10088 A JP 4068285 B JP 58059914 A LU 84291 A PT 75310 B US 5260306 A ZA 8205222 A	06/12/84 10/02/83 24/01/83 21/05/85 29/08/86 26/11/90 25/01/83 16/02/83 25/01/83 04/02/83 23/03/83 12/02/88 02/11/92 09/04/83 07/02/83 29/11/85 09/11/93 25/05/83
US 5551489 A	03/09/96	AU 7826194 A CZ 9600942 A EP 0721331 A FI 961430 A HU 74519 A HU 9600821 D IL 111080 D NO 961290 A PL 313765 A SE 9303214 D SE 9304271 D WO 9509615 A ZA 9407533 A AU 679789 B BR 9407686 A IL 113023 D JP 9504224 T SE 9400896 D SK 39196 A CN 1132476 A	01/05/95 12/06/96 17/07/96 29/03/96 28/01/97 00/00/00 00/00/00 29/03/96 22/07/96 00/00/00 00/00/00 13/04/95 03/04/95 10/07/97 04/02/97 00/00/00 28/04/97 00/00/00 04/06/97 02/10/96